



# Lost in Translation: No Effect of a High#Profile Publication on the Concomitant Use of Interacting Drugs

## Citation

Acton, Emily K., Charles E. Leonard, Warren B. Bilker, Shobha Phansalkar, and Sean Hennessy. 2017. "Lost in Translation: No Effect of a High#Profile Publication on the Concomitant Use of Interacting Drugs." *Clinical and Translational Science* 10 (6): 426-430. doi:10.1111/cts.12494. <http://dx.doi.org/10.1111/cts.12494>.

## Published Version

doi:10.1111/cts.12494

## Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:34493225>

## Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

## Share Your Story

The Harvard community has made this article openly available.  
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

## BRIEF REPORT

# Lost in Translation: No Effect of a High-Profile Publication on the Concomitant Use of Interacting Drugs

Emily K. Acton<sup>1,2</sup>, Charles E. Leonard<sup>2,3</sup>, Warren B. Bilker<sup>2,3</sup>, Shobha Phansalkar<sup>4</sup> and Sean Hennessy<sup>2,3,5,\*</sup>

We sought to assess whether a high-profile publication that demonstrated serious clinical consequences of specific drug-drug interactions (DDIs) reduced the concomitant use of those drugs. We conducted a quasi-experimental study using 2000–2008 prescription claims from a commercial health insurer to examine trends in the dispensing of the interacting drug pairs (angiotensin-converting enzyme inhibitors[ACEI] + potassium-sparing diuretic, digoxin + clarithromycin, and glyburide + cotrimoxazole) and control drug pairs previously reported in a top-tier general medicine journal. We examined prepublication and postpublication dispensing trends using Poisson regression. ACEI + potassium-sparing diuretic use did not differ postpublication vs. prepublication ( $P = 0.11$ ). Digoxin + clarithromycin use decreased minimally postpublication vs. prepublication (relative rate = 0.9996; 95% confidence interval [CI] = 0.9993–0.9998). Glyburide + cotrimoxazole use increased minimally postpublication vs. prepublication (relative rate = 1.0220; 95% CI = 1.0187–1.0254). Therefore, the high-profile DDI publication had minimal to no measurable effect in reducing the concomitant use of the interacting drugs studied. We believe that better strategies are needed to translate knowledge about DDIs into clinical practice.

*Clin Transl Sci* (2017) 10, 426–430; doi:10.1111/cts.12494; published online on 28 July 2017.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ DDIs are a major cause of avoidable morbidity and mortality, and their ongoing frequency suggests a lack of translation of research findings into clinical practice.

### WHAT QUESTION DID THIS STUDY ADDRESS?

✓ We sought to examine the impact of a high-profile DDI publication on trends in the concomitant use of the interacting drug pairs analyzed.

### WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ A high-impact DDI publication had minimal to no effect on the concomitant use of the adversely interacting drug pairs that it analyzed.

### HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

✓ These findings may emphasize the need for increased focus on improving the overall quality and signal-to-noise ratio in DDI knowledge bases.

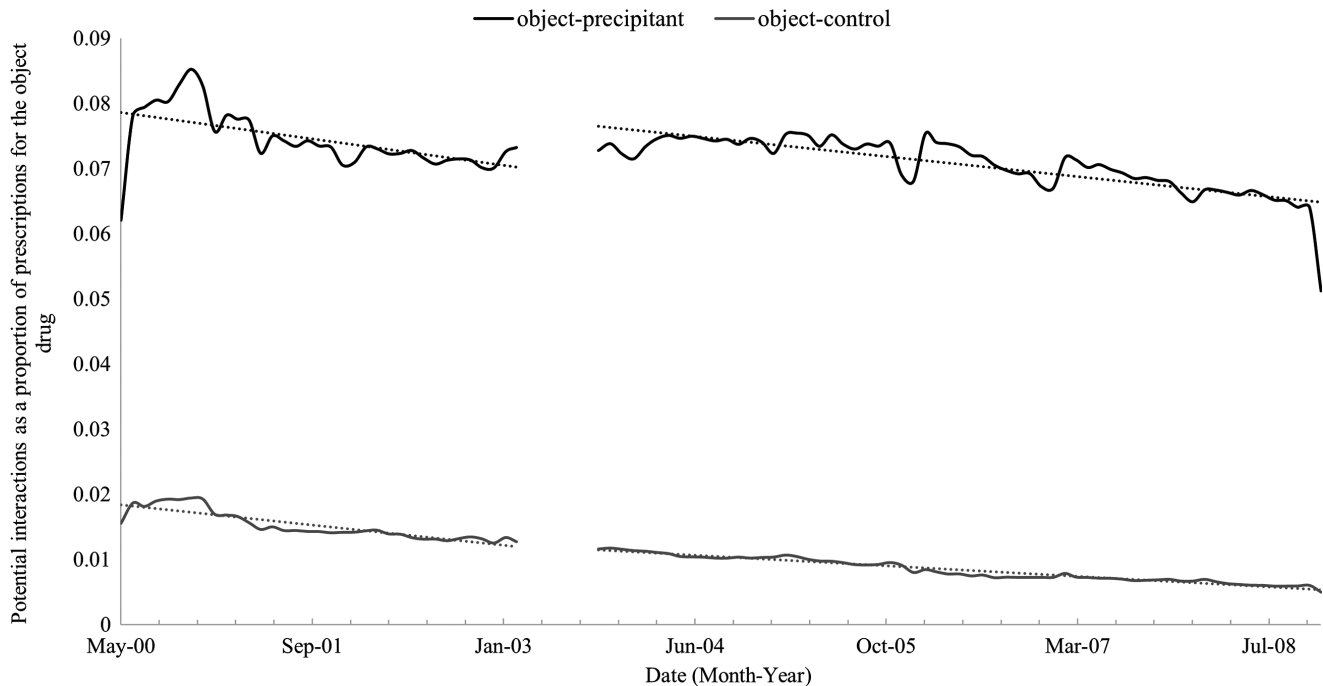
Drug-drug interactions (DDIs) are a major cause of avoidable morbidity and mortality, contributing to 1.1% of hospital admissions and 0.1% of outpatient or emergency visits to the hospital.<sup>1</sup> Major contributory factors in the high frequency of adverse DDIs are the significant discordance between DDI knowledge bases<sup>2</sup> and the estimated 90% of DDI alerts that are overridden.<sup>3</sup> These findings may suggest a problem with translating research about DDIs into clinical practice. However, this has proven to be a complex problem to study, given the ongoing changes to clinical practice combined with the rapid rate of evolution of DDI knowledge bases and computerized clinical decision support (CDS) systems.<sup>2,4</sup> To explore this problem, we selected a single, high-impact publication by Juurlink *et al.*,<sup>5</sup> which reported three sets of DDIs that

had been previously identified but not confirmed in controlled studies of health outcomes (glyburide + cotrimoxazole; digoxin + clarithromycin; and angiotensin-converting enzyme inhibitors (ACEI) + potassium-sparing diuretic) to be strongly associated (odds ratios = 6.6–20.3) with hospitalization for adverse drug events.<sup>5,6</sup> We sought to determine if this large-scale epidemiological study demonstrating the substantial risks posed by these interacting drug pairs affected the frequency of their concomitant use.

## MATERIALS AND METHODS

We conducted a quasi-experimental study using 2000–2008 prescription claims from a large US commercial health

<sup>1</sup>Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; <sup>2</sup>Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; <sup>3</sup>Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; <sup>4</sup>Department of General Medicine and Primary Care, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; <sup>5</sup>Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. \*Correspondence: S Hennessy ([hennessy@upenn.edu](mailto:hennessy@upenn.edu))  
Received 20 April 2017; accepted 4 July 2017; published online on 28 July 2017. doi:10.1111/cts.12494



**Figure 1** Overall trends in the concomitant use of target\* vs. control\*\* drug pairs. \*Target drug pairs refer to the interacting drug pairs, or the object-precipitant drug pairs, with the object drug being defined as the affected drug (i.e., glyburide, digoxin, and ACEI), and the precipitant drug being defined as the affecter drug (i.e., cotrimoxazole, clarithromycin, potassium-sparing diuretic).<sup>7</sup> \*\*Control drug pairs refer to the control, noninteracting drug pairs.

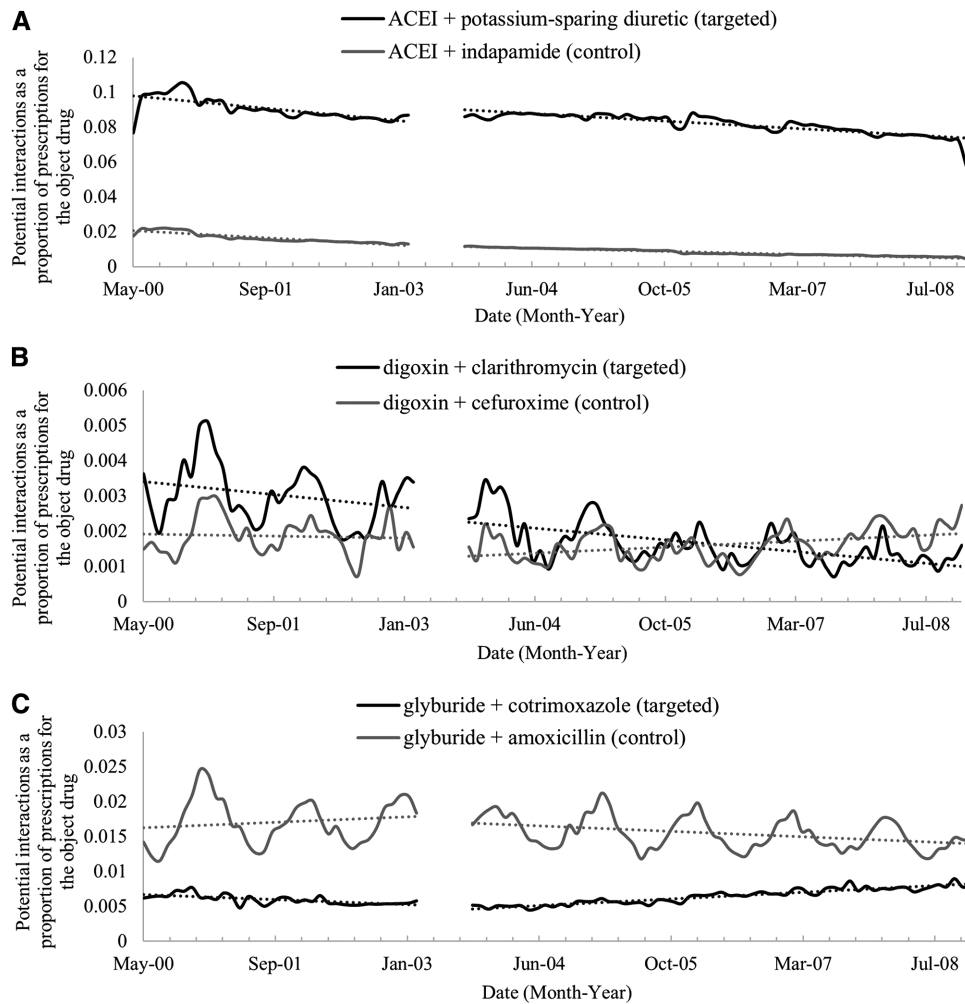
insurer (Clinformatics Data Mart, OptumInsight, Eden Prairie, MN). We examined discontinuity between prepublication and postpublication trends in the frequency of concomitant use of the following target drug pairs reported by Juurlink *et al.*<sup>5</sup> to be strongly associated with hospitalization for adverse drug events: ACEI + potassium-sparing diuretic; digoxin + clarithromycin; and glyburide + cotrimoxazole. For each DDI, the object drug was defined as the affected drug (i.e., ACEI, digoxin, and glyburide), and the precipitant drug was defined as the affecter drug (i.e., potassium-sparing diuretic, clarithromycin, and cotrimoxazole).<sup>7</sup> As control pairs, we examined trends in the object drugs' concomitant use with the noninteracting control drugs used in the Juurlink *et al.*<sup>5</sup> (2003) publication: ACEI + indapamide; digoxin + cefuroxime; and glyburide + amoxicillin. These control pairs are not believed to interact.

We defined concomitant use by assessing overlap in the dispensing of typical duration of use of prescriptions for each object-precipitant or control drug pair. We assumed that antibiotic prescriptions lasted for 10 days and that nonantibiotic prescriptions lasted for 30 days. The prepublication period was May 2000–March 2003, ending when the Juurlink *et al.*<sup>5</sup> paper was published. We assumed that any effects of publication on prescribing would take at least 6 months to occur, so we excluded April–September 2003. The postpublication period was October 2003–December 2008. We used Poisson regression to assess the prepost change in slope for the target vs. control pairs, an interaction between time period and group, examined collectively and individually.

This study was approved by the University of Pennsylvania Institutional Review Board.

## RESULTS

Utilizing prescription claims from a large US commercial health insurer obtained between 2000 and 2008, we examined discontinuity in trends between prepublication and postpublication frequency of concomitant use of the interacting drug pairs analyzed in Juurlink *et al.*<sup>5</sup> For each of these interacting drug pairs, the object drug is defined as the affected drug (i.e., ACEI, digoxin, or glyburide), and the precipitant drug is defined as the affecter drug (i.e., potassium-sparing diuretic, clarithromycin, or cotrimoxazole).<sup>7</sup> **Figure 1**<sup>7</sup> presents the collective trends in the use of target (i.e., interacting and object-precipitant) and control (i.e., noninteracting) drug pairs. Visually, the target and control pairs demonstrated similar trends of use, and there was no statistically significant difference in postpublication vs. prepublication trends between the combination of all target vs. all control drug pairs ( $P = 0.24$ ). **Figure 2** presents trends for individual drug pairs. Publication was not accompanied by a change in the use of ACEI + potassium-sparing diuretic vs. the control pair, ACEI + indapamide ( $P = 0.11$ ). Publication was associated with a 0.04% reduction in the use of digoxin + clarithromycin vs. the control pair, digoxin + cefuroxime (relative rate = 0.9996; 95% CI = 0.9993–0.9998), although that relative reduction seems to be due to an increase in postpublication use of digoxin + cefuroxime rather than a change in the declining prepublication trend in digoxin + clarithromycin (**Figure 2b**). Publication was paradoxically associated with a 2.20% increase in use of glyburide + cotrimoxazole vs. the control pair, glyburide + amoxicillin (relative rate = 1.0220; 95% CI = 1.0187–1.0254).



**Figure 2** Pair-specific trends in the concomitant use of target vs. control drug pairs. (a) Angiotensin-converting enzyme inhibitors (ACEI) + potassium-sparing diuretic and ACEI + indapamide: ACEI + potassium-sparing diuretic did not have a significant change in concomitant use in the prepublication vs. postpublication periods ( $P = 0.11$ ). (b) Digoxin + clarithromycin and digoxin + cefuroxime: digoxin + clarithromycin were less likely to be used concomitantly in the postpublication vs. prepublication period ( $P < 0.001$ ; relative rate = 0.9996; 95% confidence interval [CI] = 0.9993–0.9998). (c) Glyburide + cotrimoxazole and glyburide + amoxicillin: glyburide + cotrimoxazole were more likely to be used concomitantly in the postpublication vs. prepublication period ( $P < 0.001$ ; relative rate = 1.0220; 95% CI = 1.0187–1.0254).

## DISCUSSION

We found that publication of a high-profile epidemiologic study demonstrating serious clinical consequences of three target DDIs had minimal to no measurable effect on concomitant use of the hazardous drug pairs. The publication had no apparent overall effect on the combination of the three drug pairs' concomitant usage trends, and no apparent effect on the concomitant use of ACEI + potassium-sparing diuretic. Moreover, we found the concomitant use of glyburide + cotrimoxazole increased by 2.2% following publication. In fact, the only evidence we found suggesting the Juurlink *et al.*<sup>5</sup> publication had any impact on clinical prescribing practices was an extremely modest 0.04% reduction in the trend of digoxin + clarithromycin concomitant use following publication. This apparent reduction seemed

to be due to an increase in postpublication use of digoxin + cefuroxime rather than a change in the declining prepublication trend in digoxin + clarithromycin.

Strengths of this study include that it examined a large, representative US commercial health insurance database, used objective measurements of concomitancy, and tracked longitudinal trends in concomitant use to estimate the impact of the published article. We selected the Juurlink *et al.*<sup>5</sup> publication as our focus because it explored DDIs among commonly utilized medications, and because of its high visibility, with publication in a top-tier journal, 684 citations (by 22 June 2017), and an Altmetric score in the top 5% of all scored articles. It is important to acknowledge that, in many cases, it may not be appropriate to expect a single high-visibility study to impact clinical practice. At the time of the Juurlink *et al.*<sup>5</sup> publication (as well as prior to May 2000, the

start of our prepublication trend analysis), the potential for all three drug pairs to interact was already reported in product labels,<sup>6</sup> although no controlled studies had yet confirmed the existence or magnitude of the health risks associated with their concomitant administration. Given that prescriber knowledge of DDIs during the study period was shown to be poor,<sup>8</sup> we had hoped that a high-profile paper demonstrating and quantifying large-magnitude, serious risks would have a measurable impact on the concomitant use of the interacting drugs. Although it is possible that some prescribers managed the risks by monitoring serum potassium concentration, serum digoxin concentration, or serum glucose, two of the three interactions involve antibiotics that are typically given for a short course, making it seemingly less likely that enhanced monitoring over a few days would have been an effective strategy to manage the risks of these DDIs.

What could explain health care's apparent failure to translate the results from the Juurlink *et al.*<sup>5</sup> publication into practice? Given the enormous number of drug combinations that must be scrutinized to avoid DDIs in clinical practice, and prescribers' poor knowledge of DDIs,<sup>8</sup> computerized CDS systems are relied upon heavily. During the 2000–2008 study period, CDS systems with DDI alerts were not universally available in the United States, particularly among smaller hospitals and office practices.<sup>9</sup> Moreover, even when CDS was available, many other barriers to use have been found, including the lack of any of the following: available hardware, sufficient technical support, integration of the system into clinical workflow, timeliness of the clinical messages provided, clear articulation of the system's benefits in patient care, and minimizing perceived threats to professional autonomy.<sup>10</sup> These findings are further supported by survey data obtained in 2005 suggesting that the primary source of alerts about potential DDIs for many prescribers were pharmacists, rather than CDS systems.<sup>8</sup> Further, for DDI alerting, these barriers are compounded by the proprietary knowledge bases that screen for DDIs having an unknown time lag for incorporating new findings, being incomplete,<sup>11</sup> mostly disagreeing with one another,<sup>2</sup> and being shown to "generate excessive number[s] of alerts, many of which are clinically unhelpful."<sup>12</sup> This excessive number of alerts results in alert fatigue and attendant reflexive overriding of alerts, contributing to the ~90% of DDI alerts that are overridden.<sup>3</sup> Translating knowledge from studies of the health effects of DDIs into clinical practice may, therefore, require improving the overall quality and signal-to-noise ratio of DDI knowledge bases.

Our study has limitations. The database used only recorded prescriptions dispensed in the outpatient setting. Thus, we cannot draw conclusions about the impact of the publication by Juurlink *et al.*<sup>5</sup> on: (a) ambulatory prescriptions that were never filled (i.e., primary nonadherence); or (b) inpatient dispensing. Additionally, it is possible that our study underestimated the clinical impact of the publication by focusing on concomitant dispensing trends rather than DDI-related adverse events. It is also noteworthy that the Juurlink *et al.*<sup>5</sup> paper focused exclusively on the occurrence of DDIs in people 66 years of age or older, as necessitated by their use of the Ontario Drug Benefit Program claims. As our focus was on the impact of this paper, we elected to more

broadly examine the overall trends in concomitant prescription regardless of recipient ages, as we felt this publication would have had impact outside of its analyzed age range.

With the rapid pace of CDS and knowledge base evolution,<sup>2,4</sup> and potential differences in CDS availability internationally,<sup>8</sup> further research is needed to understand the generalizability of our conclusions. Also, we elected to utilize the same control drug pairs as Juurlink *et al.*,<sup>5</sup> because there is no literature to suggest interactions between the control drug pairs. However, selecting optimal controls for this sort of study is inherently challenging, given that drug trends over time can be difficult to predict or even fully account for in retrospect potentially introducing bias into our findings. Finally, although we are aware of no major publications or large-scale health practice changes that would have directly affected the frequency of co-administration of the drugs studied, it is possible there may have been other literature or clinical practice changes that impeded the translation of the Juurlink *et al.*<sup>5</sup> publication into clinical practice. For example, a subsequent study by Juurlink *et al.*<sup>13</sup> (2004), reported that when the randomized aldactone evaluation study (1999) demonstrated that spironolactone use reduces morbidity and mortality in patients with severe heart failure,<sup>14</sup> an increase in adverse events associated with the concomitant use of aldosterone and ACEIs was observed. These limitations present important areas for future studies to explore.

Our study found that a high-impact publication demonstrating substantial risks associated with DDIs had minimal to no effect on the concomitant use of the adversely interacting drug pairs that it analyzed. This suggests a lack of translation of research findings into clinical practice. A crucial step in reducing drug-related adverse events may be to improve the overall quality and signal-to-noise ratio in DDI knowledge bases.

**Source of Funding.** Supported by grants R01AG025152 and R01OK102694 from the US National Institutes of Health.

**Author Contributions.** S.H., E.A., C.E.L., W.B.B., and S.P. wrote the manuscript. S.H., E.A., C.E.L., and W.B.B. designed the research. S.H., E.A., C.E.L., W.B.B., and S.P. performed the research. S.H., E.A., C.E.L., and W.B.B. analyzed the data.

**Conflict of Interest.** W.B.B. has received consulting money from Janssen Pharmaceutical. S.P. is Director of Innovation and Clinical Informatics in the Clinical Drug Information division of Wolters Kluwer Health. S.H. reports grants from US National Institutes of Health, during the conduct of the study; personal fees from Merck Sharp & Dohme Corp, outside the submitted work. E.A. and C.E.L. have no conflicts to declare.

1. Dechanont, S., Maphanta, S., Butthum, B. & Kongkaew, C. Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. *Pharmacoepidemiol. Drug Saf.* **23**, 489–497 (2014).
2. Ayvaz, S. *et al.* Toward a complete dataset of drug-drug interaction information from publicly available sources. *J. Biomed. Inform.* **55**, 206–217 (2015).
3. Ridgely, M.S. & Greenberg, M.D. Too many alerts, too much liability: sorting through the malpractice implications of drug-drug interaction clinical decision support. *St. Louis University Journal of Health Law & Policy*. **5**, 257–296. [http://www.rand.org/pubs/external\\_publications/EP201200144.html](http://www.rand.org/pubs/external_publications/EP201200144.html) (2012).
4. Middleton, B., Sittig, D.F. & Wright, A. Clinical decision support: a 25 year retrospective and a 25 year vision. *Yearb. Med. Inform. Suppl* **1**, S103–S116 (2016).

5. Juurlink, D.N., Mamdani, M., Kopp, A., Laupacis, A. & Redelmeier, D.A. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* **289**, 1652–1658 (2003).
6. Medical Economics. *1999 Physicians' Desk Reference* 53rd edn. (PDR Network, LLC, Montvale, NJ, 1999).
7. Hennessy, S. et al. Pharmacoepidemiologic methods for studying the health effects of drug-drug interactions. *Clin. Pharmacol. Ther.* **99**, 92–100 (2016).
8. Ko, Y. et al. Prescribers' knowledge of and sources of information for potential drug-drug interactions: a postal survey of US prescribers. *Drug Saf.* **31**, 525–536 (2008).
9. Greenes, R.A. A brief history of clinical decision support. In *Clinical Decision Support: The Road to Broad Adoption* (ed. Greenes, R.A.) 49–110 (Elsevier Inc., San Diego, CA, 2014).
10. Moxey, A., Robertson, J., Newby, D., Hains, I., Williamson, M. & Pearson, S.A. Computerized clinical decision support for prescribing: provision does not guarantee uptake. *J. Am. Med. Inform. Assoc.* **17**, 25–33 (2010).
11. Wang, L.M., Wong, M., Lightwood, J.M. & Cheng, C.M. Black box warning contraindicated comedications: concordance among three major drug interaction screening programs. *Ann. Pharmacother.* **44**, 28–34 (2010).
12. Kuperman, G.J., Reichley, R.M. & Bailey, T.C. Using commercial knowledge bases for clinical decision support: opportunities, hurdles, and recommendations. *J. Am. Med. Inform. Assoc.* **13**, 369–371 (2006).
13. Juurlink, D.N. et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N. Engl. J. Med.* **351**, 543–551 (2004).
14. Pitt, B. et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med.* **341**, 709–717 (1999).

© 2017 The Authors. Clinical and Translational Science published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Supplementary information accompanies this paper on the *Clinical and Translational Science* website.  
([http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1752-8062](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1752-8062))